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Clinical and genetic factors associated with disease course in inflammatory bowel disease

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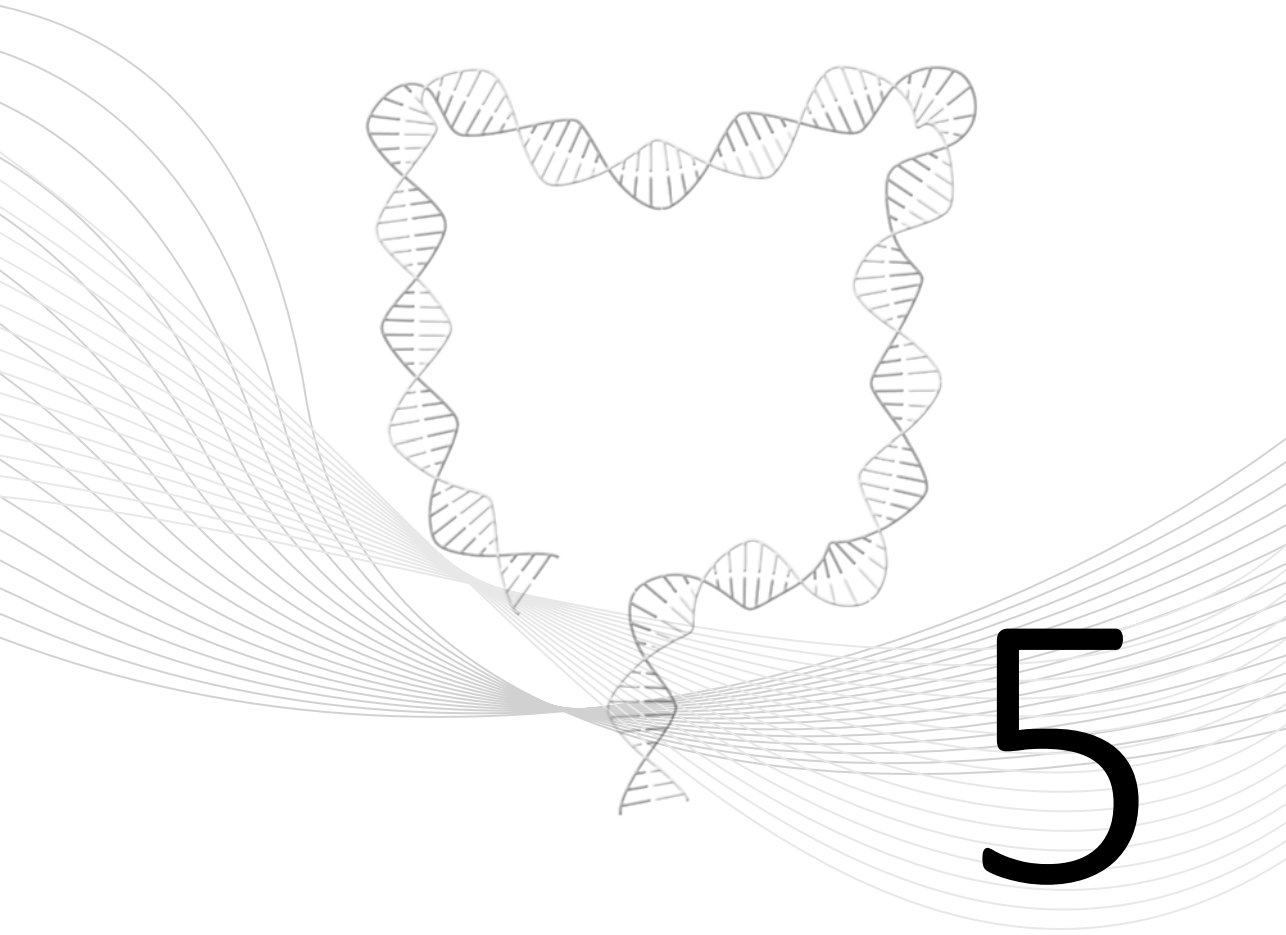

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The impact of ethnicity and country of birth on inflammatory bowel disease phenotype: a prospective cohort study

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on behalf of the Parelsnoer Institute (PSI) and the Dutch Initiative on Crohn and Colitis (ICC)
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Abstract

Background: The number of patients with inflammatory bowel disease (IBD), of non-Caucasian descent in Western Europe, is increasing. We aimed to explore the impact of ethnicity and country of birth on IBD phenotype.

Methods: IBD patients treated in the eight University Medical Centers in the Netherlands (Dutch IBD Biobank) were divided into two groups according to their ethnicity: 1) Caucasian patients of Western and Central European descent (CEU); and 2) patients of non-Caucasian descent (non-CEU). The non-CEU group was subdivided according to country of birth, into: born in the Netherlands or Western Europe (non-CEU European born); or born outside Western-Europe who migrated to the Netherlands (non-CEU non-European born). Both comparisons were analysed for phenotype differences (by chi-square test).

Results: The Dutch IBD Biobank included 2921 CEU patients and 233 non-CEU patients. Non-CEU Crohn's disease (CD) patients more often had upper gastro-intestinal disease (16% vs 8%, P = 0.001) and anal stenosis (10% vs 4%, P = 0.002) than CEU CD patients. The use of anti-tumour necrosis factor (TNF) agents and immunomodulators was higher in non-CEU IBD patients than in CEU IBD patients (45% vs 38%, P = 0.042) and (77% vs 66%, P = 0.001), respectively. Non-CEU IBD patients born in Europe (*n* = 116) were diagnosed at a lower age than non-CEU IBD patients born outside Europe (*n* = 115) (at 22.7 vs 28.9 years old, P < 0.001).

Conclusion: Non-Caucasians had more severe disease behaviour than Caucasians. Non-CEU patients born in Europe were diagnosed at a lower age with IBD than those born outside Europe who migrated to the Netherlands.

Introduction

The incidence of inflammatory bowel disease (IBD) in Western Europe has remained relatively stable over recent years, but is increasing in developing countries.[1]

It is known that genetic and environmental factors play an important role in the aetiology of IBD. Over recent years, there has been tremendous progress in unravelling the genetic background of IBD, and 200 regions on the human genome have been found to be associated with IBD.[2] Still, the genetic architecture only partly explains the susceptibility to IBD, suggesting that environmental factors contribute to the development of Crohn's disease (CD) and ulcerative colitis (UC).[3] The increasing prevalence of IBD among individuals migrating from low-prevalence regions to high-prevalence regions suggests a role for environmental factors, such as a Westernised diet or lifestyle.[4-6]

Data on ethnic differences regarding phenotypic manifestations of IBD are not consistent, and most published studies so far have relatively small sample sizes.[7-11] Since the number of non-Caucasians (patients from non-European descent) with IBD is increasing in Western European countries,[12] potential phenotypic differences between Caucasian and non-Caucasian IBD patients are of increasing relevance. Treatment paradigms are based on studies predominantly conducted in the Caucasian IBD population,[13] and therefore recognition of ethnic differences in phenotypic manifestations will aid clinical decision making such as optimising individual management and tailoring treatment options. The aim of this study is therefore 2-fold: 1) to gain more insight into the phenotypic differences between Caucasian and non-Caucasian IBD patients in the Netherlands; and 2) to explore the influence of country of birth on the clinical phenotype in non-Caucasian IBD patients by comparing non-Caucasians born in Europe with non-Caucasians born in non-European countries.

Methods

Study design and study population

We conducted a multicentre analysis of IBD patients enrolled in the Dutch IBD Biobank, which is part of the Parelsnoer Institute (www.parelsnoer.org). Since 2007, every IBD patient treated in any one of the eight University Medical Centers (UMCs) is asked to participate in the Dutch IBD Biobank. The Dutch IBD Biobank collects clinical data through an information model that contains 225 IBD-related items. The IBD-related items used for this paper and their definitions can be found in **Supplementary File 1**, available as Supplementary data at *ECCO-JCC* online. These items are retrieved from medical records and are stored in a central database that can be accessed

via web-based trough as a secure transfer. IBD patients are continuously being enrolled in the Dutch IBD Biobank, and data are collected prospectively.[14] At the moment of data freeze (17 July 2014), the Dutch IBD Biobank contained 3388 IBD patients. For this study, patients were excluded if information on ethnicity was missing. Caucasian IBD patients from West or Central European descent were excluded when they were not born in the Netherlands or when their parents were not born in the Netherlands or Europe.

Cohort

The clinician addressed ethnicity/descent during consultation; patients were asked about their descent, country of birth, and country of birth of their parents.

To address the influence of ethnic differences on disease behaviour, IBD patients were divided in two broad groups according to their ethnicity (Figure 1):

1. Caucasians from West or Central European descent (CEU) born in the Netherlands;
2. patients from non-Caucasian descent (non-CEU). Although this second group consists of a heterogeneous group of ethnicities, for the current comparative analysis we will refer to this specific group as “non-CEU”.

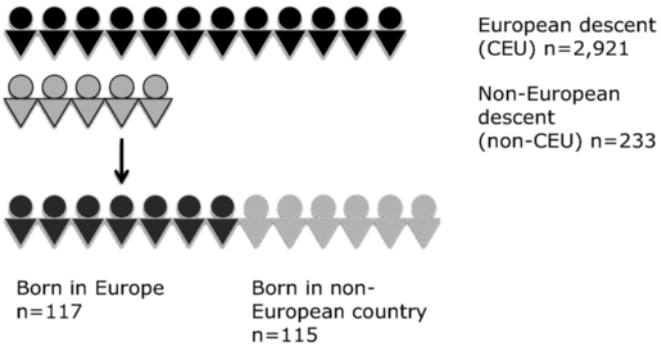

Figure 1 IBD patients were divided according to their ethnicity in two groups CEU and non-CEU. The non-CEU group was divided according to country of birth; born in Europe or born in non-European country.
IBD, inflammatory bowel disease; CEU, Central European descent.

To address the influence of country of birth on phenotypic manifestations of IBD, the second group was then subdivided in two broad groups according to country of birth (Figure 1):

- born in the Netherlands or Western Europe (non-CEU born in Europe);
- born outside Europe and migrated to the Netherlands (non-CEU born in non-European countries).

Statistical analysis

In all analyses, UC patients also included IBD-unclassified (IBD-U) and IBD-indeterminate (IBD-I) patients. Quantitative variables between the different groups were compared using the Mann-Whitney U test. Qualitative variables among the different groups were compared using the Pearson chi-square test or Fisher's exact test. We performed a survival analysis for first IBD-related surgery on time-to-event data using the date of diagnosis and the date of first IBD-related surgery that was registered at the first outpatient clinic visit. Small bowel resection, ileocaecal resection, colon resection, other resections, strictureplasty, ileostomy/colostomy, and surgery for abscesses or fistula were included as first surgery in the analysis. Kaplan-Meier curves for time free of surgery were constructed, and differences between CEU and non-CEU were assessed by the log-rank test. The cumulative proportion of IBD patients remaining free of first IBD-related surgery was calculated at 2 and 5 years after IBD diagnosis. We performed a multivariate Cox proportion hazards analysis for time to first IBD-related surgery for all IBD patients. We corrected for covariates with a P value < 0.05 in the univariate analysis gender (female/male), age, smoking status, ileocolonic disease (L3), extensive colitis (E3), fistulising disease, stricturing disease, penetrating disease, anti-tumour necrosis factor (TNF) use, and immunomodulator use) or when the proportional-hazards assumption was not met. Statistical analyses were performed with Stata Software V.13.1.[15]

Results

Patient population

In total 3154 IBD patients were included in this study (1968 CD, 1108 UC, 72 IBD-U, and 6 IBD-I patients). Of these, 2921 patients were from CEU descent (born in the Netherlands) and 233 patients were from non-CEU descent. Of these 233 patients, 117 patients were from non-CEU descent born in Europe and 115 patients were from non-CEU descent born in non-European countries (for descent and country of birth see **Supplementary File 2**, available as Supplementary data at *ECCO-JCC* online). Parents' countries of origin for the 117 non-CEU descent IBD patients born in Europe are depicted in **Supplementary File 3**, available as Supplementary data at *ECCO-JCC* online.

1. Phenotypic differences between CEU and non-CEU IBD patients

Demographic differences between CEU and non-CEU IBD patients

There were no differences in IBD diagnosis or sex ratio between CEU patients and non-CEU patients. Non-CEU patients were younger at time of inclusion than CEU patients (37.5 vs 42.9 years, P < 0.001).

The median disease duration at inclusion was longer in CEU patients than in non-CEU patients (11.6 vs 10.2 years, P = 0.038) (Table 1).

Age at diagnosis in CEU and non-CEU IBD patients

There was no statistically significant difference in age at diagnosis between CEU patients and non-CEU patients (26.5 vs 25.8 years, P = 0.053) (Table 1).

Table 1 Demographic differences between IBD patients of CEU and non-CEU descent.

	CEU	Non-CEU
n (%)	2921 (100%)	233 (100%)
Sex	2921 (100%)	233 (100%)
Male	1213 (42%)	84 (36%)
Female	1708 (58%)	149 (64%)
Diagnosis	2921 (100%)	233 (100%)
Crohn's disease	1825 (62%)	143 (61%)
UC/IBD-U/IBD-I	1096 (38%)	90 (39%)
Disease characteristics		
Age of inclusion median years (IQR 25-75)	42.9 (32-55)	37.5 (30-49)**
Median Age Diagnosis years (IQR 25-75)	26.5 (20-37)	25.8 (19-33)
Median Disease duration years (IQR 25-75)	11.6 (5-20)	10.2 (5-17)*
Primary sclerosing cholangitis (PSC)[†]	64 (2%)	3 (1.3%)
Family history of IBD[†]	828 (28%)	56 (24%)
Appendectomy[†]	346 (12%)	18 (8%)

[†]Missing values were scored as non-present;
*P < 0.05; **P < 0.001.
CEU: central European descent; UC: ulcerative colitis; IBD-U: inflammatory bowel disease unclassified; IBD-I: inflammatory bowel disease indeterminate; IBD: inflammatory bowel disease; IQR: interquartile range.

Disease behaviour in CEU and non-CEU IBD patients

According to the Montreal classification, division of disease location (L) in CD did not differ between CEU patients and non-CEU patients. Upper gastro-intestinal disease was more common in non-CEU patients than in CEU patients with CD (16% vs 8%, P = 0.001). Disease behaviour in CD was similar between CEU patients and non-CEU patients, except for anal stenosis, which was more common in non-CEU patients (10% vs 4%, P = 0.002). **Supplementary File 4, Table 1** (available as Supplementary data at *ECCO-JCC* online) shows no statistically significant differences in upper gastro-intestinal disease or anal stenosis in a subanalysis between the three largest non-CEU groups (African, Hindustani, Turkish).

No difference was found in disease localisation in UC between CEU patients and non-CEU patients (Table 2).

Medication use in CEU and non-CEU IBD patients

The use of anti-TNFα agents was more frequent in non-CEU IBD patients than in CEU IBD patients (45% vs 38%, P = 0.042). The use of anti-TNFα agents was more frequent in non-CEU patients with UC compared with CEU patients with UC (28% vs 19%, P = 0.047). Immunomodulators were more often used in non-CEU IBD patients than in CEU IBD patients (77% vs 66%, P = 0.001). **Supplementary File 4, Table 1** shows no statistically significant differences in the use of anti-TNFα agents or the use of immunomodulators in a subanalysis between the three largest non-CEU groups (African, Hindustani, Turkish). The use of azathioprine and 6-thioguanine was higher among non-CEU IBD patients than CEU IBD patients (58% vs 49%, P = 0.010) and (7% vs 3%, P = 0.010), respectively. This higher use of azathioprine and 6-thioguanine was predominantly found in non-CEU patients with UC compared with CEU patients with UC (57% vs 41%, P = 0.003) and (11% vs 4%, P = 0.001), respectively (Table 3).

Surgery rates in CEU and non-CEU IBD patients

There was no statistically significant difference in overall surgery rates and the number of stoma and pouches between CEU patients and non-CEU patients (**Supplementary File 4, Table 2**).

At 2 years after IBD diagnosis, the proportion of IBD patients who remained free of IBD surgery was 84% (95% confidence interval (CI): 83%-86%) in CEU patients and 91% (95% CI: 86%-94%) in non-CEU patients (Figure 2). At 5 years after IBD diagnosis, the proportion of IBD patients who remained free of surgery was 74% (95% CI: 72%-76%) in CEU patients and 75% (95% CI: 68%-80%) in non-CEU patients (no statistically significant difference, log-rank test, P = 0.900).

No increased risk of first IBD-related surgery for CEU patients compared with non-CEU patients was found (hazard ratio (HR) 1.01, 95% CI: 0.81-1.27). The multivariate model showed that ileocolonic involvement (L3) (HR 1.48, 95% CI: 1.27-1.72), extensive colitis (E3) (HR 1.18, 95% CI: 1.02-1.38), fistulising disease (HR 1.71, 95% CI: 1.43-2.03), stricturing disease (HR 2.01, 95% CI: 1.72-2.35), penetrating disease (HR 2.35, 95% CI: 1.96-2.81) and anti-TNFα use (HR 1.15, 95% CI: 1.00-1.33) were associated with an increased risk of first IBD-related surgery (**Supplementary File 4, Table 3**).

Table 2 Disease behaviour in IBD patients of CEU and non-CEU descent.

Montreal classification	CEU	Non-CEU
Crohn's disease	1825 (100%)	143 (100%)
A1: diagnosis ≤ 16 years	263 (15%)	28 (20%)
A2: diagnosis 17-40 years	1264 (69%)	95 (66%)
A3: diagnosis > 40 years	298 (16%)	20 (14%)
L1: ileal disease[a]	335 (23%)	27 (25%)
L2: colon disease[a]	451 (31%)	29 (26%)
L3: ileocolon disease[a]	682 (46%)	54 (49%)
L4: upper GI disease[†]	149 (8%)	23 (16%)*
P: peri-anal disease[†]	494 (27%)	35 (24%)
Ulcerative colitis disease		
E1: proctitis[b]	77 (8%)	6 (9%)
E2: left-sided colitis[b]	325 (35%)	21 (31%)
E3: extensive colitis[b]	533 (57%)	41 (60%)
Disease behaviour CD	1825 (100%)	143 (100%)
Fistulising disease		
Enterocutaneous fistula[†]	91 (5%)	8 (6%)
Entero-internal fistula[†]	159 (9%)	12 (8%)
Recto-vaginal fistula[†]	99 (5%)	9 (6%)
Stricturing disease		
Stricture[†]	444 (24%)	28 (20%)
Anal stenosis[†]	75 (4%)	14 (10%)*
Penetrating disease		
Intestinal perforation[†]	52 (3%)	5 (4%)
Intestinal abscess[†]	195 (11%)	17 (12%)

[a]These percentages are calculated for 1468 CEU patients and 110 non-CEU patients with CD;
[b]These percentages are calculated for 935 CEU patients and 68 non-CEU with UC;
[†]Missing values were scored as non-present;
*P < 0.01.
IBD: inflammatory bowel disease; CEU: central European descent; CD: Crohn's disease; GI: gastro-intestinal.

Extraintestinal manifestations in CEU and non-CEU IBD patients

There were no statistically significant differences in the prevalence of skin manifestations, musculoskeletal manifestations, ocular manifestations, osteopenia, or thromboembolic events between CEU patients and non-CEU patients (**Supplementary File 4, Table 4**).

Additional analysis; including all CEU patients independently of country of birth

CEU patients born outside the Netherlands (*n* = 96) were included in the CEU patient group, bringing the total to 3090 CEU IBD patients. Our main findings (i.e., upper gastro-intestinal (GI) disease L4, anal stenosis, anti-TNF use and immunomodulator use) remained statistically significant in these analyses (P < 0.05) comparing CEU and non-CEU patients.

Table 3 Medication use in IBD patients from CEU and non-CEU descent.

	CEU	Non-CEU
Medication use during disease	2861 (100%)	230 (100%)
Anti-TNF[c]	1087 (38%)	103 (45%)*
Anti-TNF CD[a]	880 (49%)	78 (55%)
Anti-TNF UC[b]	207 (19%)	25 (28%)*
Immunomodulators[d]	1898 (66%)	177 (77%)***
Immunomodulators CD[a]	1302 (73%)	114 (81%)*
Immunomodulators UC[b]	596 (56%)	63 (71%)**
Mercaptopurine[e]	463 (16%)	47 (20%)
Mercaptopurine CD[a]	316 (18%)	29 (21%)
Mercaptopurine UC[b]	147 (14%)	18 (20%)
Azathioprine[f]	1413 (49%)	134 (58%)*
Azathioprine CD[a]	971 (54%)	83 (59%)
Azathioprine UC[b]	442 (41%)	51 (57%)**
Thioguanine[g]	94 (3%)	15 (7%)*
Thioguanine CD[a]	53 (3%)	5 (4%)
Thioguanine UC[b]	41 (4%)	10 (11%)***
Methotrexate[h]	365 (13%)	34 (15%)
Methotrexate CD[a]	313 (18%)	28 (20%)
Methotrexate UC[b]	52 (5%)	6 (7%)

[a]These percentages are calculated for 1789 CEU patients and 141 non-CEU patients with CD;
[b]These percentages are calculated for 1072 CEU patients and 89 non-CEU patients with UC;
[c]Anti-TNF: patients used infliximab, adalimumab or certolizumab;
[d]Immunomodulators: patients used mercaptopurine, Puri-nethol, azathioprine, Imuran, thioguanine, methotrexate or Methoject;
[e]Mercaptopurine: patients used mercaptopurine or Puri-nethol;
[f]Azathioprine: patients used azathioprine or Imuran;
[g]Thioguanine: patients used thioguanine or Lanvis;
[h]Methotrexate: patients used methotrexate or Methoject;
*P < 0.05; **P < 0.01; ***P = 0.001.
IBD: inflammatory bowel disease; CEU: central European descent; CD: Crohn's disease; UC: ulcerative colitis; TNF: tumour necrosis factor.

2. Phenotypic differences between non-CEU IBD patients born in Europe and non-CEU IBD patients born in non-European countries who migrated to the Netherlands

Demographic differences between non-CEU IBD patients born in Europe and non-CEU IBD patients born in non-European countries

There were no differences in IBD diagnosis or sex-ratio between non-CEU patients born in Europe and non-CEU patients born in non-European countries. Non-CEU patients born in Europe were younger at time of inclusion than non-CEU patients born in non-European countries (32.0 vs 43.1

years, P < 0.001). The median disease duration at inclusion was longer in non-CEU patients born in non-European countries compared with European countries (11.7 vs 8.0 years, P = 0.006) (Table 4).

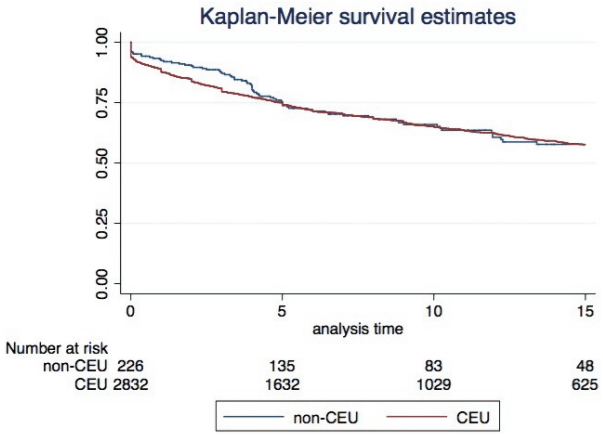

Figure 2 Kaplan-Meier curve; time till first IBD = related surgery compared between CEU and non-CEU patients.

Age at diagnosis in non-CEU IBD patients born in Europe and non-CEU IBD patients born in non-European countries

Non-CEU IBD patients born in Europe were diagnosed at a lower age than non-CEU IBD patients born in non-European countries who migrated to the Netherlands (22.7 vs 28.9 years old, P < 0.001) (Table 4).

Disease behaviour in non-CEU IBD patients born in Europe and non-CEU IBD patients born in non-European countries

Non-CEU patients born in Europe were diagnosed with IBD before the age of 17 years more often compared with non-CEU patients born in non-European countries (29% vs 9%, P = 0.002). Non-CEU patients born in non-European countries were more often diagnosed with IBD after the age of 40 years (22% vs 7%, P = 0.008). According to the Montreal classification, division of disease location (L) in CD did not differ between non-CEU patients born in Europe and non-CEU patients born in non-European countries. No difference was found in disease localisation in UC between non-CEU patients born in Europe and non-CEU patients born in non-European countries (Table 5).

Table 4 Demographic differences between non-CEU IBD patients born in Europe and non-CEU IBD patients born in non-European countries.

	NL/EU born	born non-European country
n (%)	117 (50%)	115 (50%)
Sex	117 (100%)	115 (100%)
Male	43 (37%)	40 (35%)
Female	74 (63%)	75 (65%)
Diagnosis	117 (100%)	115 (100%)
Crohn's disease	75 (64%)	68 (59%)
UC/IBD-U/IBD-I	42 (36%)	47 (41%)
Disease characteristics		
Age of inclusion median years (IQR 25-75)	32.0 (26-44)	43.1 (36-55)**
Median Age Diagnosis years (IQR 25-75)	22.7 (17-29)	28.9 (23-40)**
Median Disease duration years (IQR 25-75)	8.0 (5-14)	11.7 (6-20)*
Primary sclerosing cholangitis (PSC) †	2 (1.7%)	1 (0.9%)
Family history of IBD†	30 (26%)	26 (23%)
Appendectomy†	7 (6%)	11 (10%)

†Missing values were scored as non-present;
*P < 0.01; **P < 0.001.
NL: Netherlands; EU: Europe; CEU: Central European descent; UC: ulcerative colitis; IBD-U: inflammatory bowel disease unclassified; IBD-I: inflammatory bowel disease indeterminate; IBD: inflammatory bowel disease; IQR: interquartile range.

Medication use in non-CEU IBD patients born in Europe and non-CEU IBD patients born in non-European countries

There were no differences in medication use between non-CEU IBD patients born in Europe and non-CEU IBD patients born in non-European countries. Except for the use of mercaptopurine, which was higher among non-CEU patients with UC born in non-European countries than non-CEU patients with UC born in European countries (30% vs 10%, P = 0.015) (Table 6).

Surgery rates in non-CEU IBD patients born in Europe and non-CEU IBD patients born in non-European countries

There was no statistically significant difference in overall surgery rates and the numbers of stoma and pouches between non-CEU IBD patients born in Europe and non-CEU IBD patients born in a non-European country (**Supplementary File 4, Table 5**).

Table 5 Disease behaviour in non-CEU IBD patients born in Europe and non-CEU IBD patients born in non-European countries.

Montreal classification	NL/EU born	born non-European country
Crohn's disease	75 (100%)	68 (100%)
A1: diagnosis ≤ 16 years	22 (29%)	6 (9%)*
A2: diagnosis 17-40 years	48 (64%)	47 (69%)
A3: diagnosis > 40 years	5 (7%)	15 (22%)*
L1: ileal disease[a]	15 (26%)	12 (23%)
L2: colon disease[a]	17 (30%)	12 (23%)
L3: ileocolon disease[a]	25 (44%)	29 (54%)
L4: upper GI disease[†]	11 (15%)	12 (18%)
P: peri-anal disease[†]	16 (21%)	19 (28%)
Ulcerative colitis disease		
E1: proctitis[b]	1 (3%)	4 (12%)
E2: left-sided colitis[b]	9 (26%)	12 (36%)
E3: extensive colitis[b]	24 (71%)	17 (52%)
Disease behaviour CD	75 (100%)	68 (100%)
Fistulising disease		
Enterocutaneous fistula[†]	2 (3%)	6 (9%)
Entero-internal fistula[†]	5 (7%)	7 (10%)
Recto-vaginal fistula[†]	4 (5%)	5 (7%)
Stricturing disease		
Stricture[†]	13 (17%)	15 (22%)
Anal stenosis[†]	10 (13%)	4 (6%)
Penetrating disease		
Intestinal perforation[†]	2 (3%)	3 (4%)
Intestinal abscess[†]	11 (15%)	6 (9%)

[a]These percentages are calculated for 57 non-CEU patients born in NL/EU and 53 non-CEU patients born in non-European countries with CD;
[b]These percentages are calculated for 34 non-CEU patients born in NL/EU and 33 non-CEU patients born in non-European countries with UC;
[†]Missing values were scored as non-present.
*P < 0.01.
NL: Netherlands; EU: Europe; CEU: Central European descent; CD: Crohn's disease. GI: gastro-intestinal.

Extraintestinal manifestations in non-CEU IBD patients born in Europe and non-CEU IBD patients born in non-European countries

There were no statistically significant differences in the prevalence of skin manifestations, musculoskeletal manifestations, ocular manifestations, osteopenia, or thromboembolic events between non-CEU IBD patients born in Europe and non-CEU IBD patients born in a non-European country (**Supplementary File 4, Table 6**).

Table 6 Medication use in non-CEU IBD patients born in Europe and non-CEU IBD patients born in non-European countries.

	NL/EU born	born non-European country
Medication use during disease	115 (100%)	114 (100%)
Anti-TNF[c]	56 (49%)	47 (41%)
Anti-TNF CD[a]	43 (59%)	35 (51%)
Anti-TNF UC[b]	13 (31%)	12 (26%)
Immunomodulators[d]	89 (77%)	87 (76%)
Immunomodulators CD[a]	58 (79%)	56 (82%)
Immunomodulators UC[b]	31 (74%)	31 (67%)
Mercaptopurine[e]	20 (17%)	27 (24%)
Mercaptopurine CD[a]	16 (22%)	13 (19%)
Mercaptopurine UC[b]	4 (10%)	14 (30%)*
Azathioprine[f]	69 (60%)	64 (56%)
Azathioprine CD[a]	44 (60%)	39 (57%)
Azathioprine UC[b]	25 (60%)	25 (54%)
Thioguanine[g]	7 (6%)	8 (7%)
Thioguanine CD[a]	3 (4%)	2 (3%)
Thioguanine UC[b]	4 (10%)	6 (13%)
Methotrexate[h]	17 (15%)	17 (15%)
Methotrexate CD[a]	14 (19%)	14 (21%)
Methotrexate UC[b]	3 (7%)	3 (7%)

[a]These percentages are calculated for 73 non-CEU patients born in NL/EU and 68 non-CEU patients born in non-European countries with CD;
[b]These percentages are calculated for 42 non-CEU patients born in NL/EU and 46 non-CEU patients born in non-European countries with UC;
[c]Anti-TNF: patients used infliximab, adalimumab or certolizumab;
[d]Immunomodulators: patients used mercaptopurine, Puri-nethol, azathioprine, Imuran, thioguanine, methotrexate, or Methoject;
[e]Mercaptopurine: patients used mercaptopurine or Puri-nethol;
[f]Azathioprine: patients used azathioprine or Imuran;
[g]Thioguanine: patients used thioguanine or Lanvis;
[h]Methotrexate: patients used methotrexate or Methoject;
*$P < 0.05$.
NL: Netherlands; EU: Europe; CEU: Central European descent; CD: Crohn's disease; UC: ulcerative colitis.

Discussion

In this large prospective cohort study, we aimed to explore the impact of ethnicity and country of birth on phenotype in IBD patients. We observed that non-CEU patients have more upper GI disease, more stricturing disease and use anti-TNF agents and immunomodulators more often than CEU patients. Furthermore, we found that non-CEU IBD patients born in Europe were diagnosed

at a lower age than non-CEU IBD patients born in non-European countries who migrated to the Netherlands.

Worse disease behaviour in non-CEU compared with CEU IBD patients

We found upper GI disease and anal stenosis to be more common in non-CEU patients compared with CEU patients with CD after a median disease duration of 10 years. Most studies reporting on progression of CD behaviour are conducted in Western populations.[16,17] One study compared disease behaviour between Asian and Australian patients with CD and found stricturing disease to be more common in Asians with CD at diagnosis. Furthermore, they reported a cumulative probability of 20% that CD behaviour would change from inflammatory to stricturing or penetrating disease independent of ethnicity.[9] A review from the UK showed a more severe disease in Asian migrants compared with Caucasian non-migrants.[18] In our cohort, we had six CD patients from Asian descent; one of them had an anal stenosis. However, we were not able to conduct a statistical analysis due to the small sample size. On the other hand, a large review stated that there seems to be no difference in complicated disease behaviour among IBD patients from African American, Asian, and Hispanic descent living in the USA.[19] Interestingly, a study from Belgium compared Moroccan migrants with Caucasian migrants, the latter being a diverse group of Eastern European and Middle Eastern migrants, and found a more severe disease behaviour (more penetrating disease and anti-TNF use) among Moroccan migrants.[20] It has been suggested that a more severe disease behaviour among non-Caucasians is a consequence of delayed disease presentation. However, in our study we could not detect differences in disease behaviour between non-CEU IBD patients born in Europe or non-CEU IBD patients born in non-European countries. A more severe disease behaviour due to a delayed disease presentation is therefore unlikely. To date, genetic risk variants explain only about 10% of the disease risk, which suggests that environmental factors play an important role in the disease pathogenesis. A study from England has shown that disease localisation follows the pattern of the indigenous population after one generation,[21] but other articles challenge these findings.[22] As environmental risk factors play an important role in IBD, a severe disease phenotype could therefore concur with the duration of exposure to these risk factors.

Higher use of IBD medication in non-CEU compared with CEU IBD patients

We found non-CEU IBD patients to use anti-TNF agents and immunomodulators more frequently than CEU patients. In previous studies, the use of medical therapy was similar in Asians compared with Australians.[9,23] Higher anti-TNFα use in our cohort could be explained by the more severe disease behaviour (i.e., more stricturing disease) in non-CEU patients with CD in our cohort. Indeed, a previous study found no differences in infliximab use between African Americans and Caucasian CD patients by only selecting patients with penetrating Crohn's disease.[24] There were no major

differences in extraintestinal manifestations (EIMs) or surgery rates, the latter previously being attributed to differences in health insurance status.[19] However, as inhabitants of the Netherlands all have mandatory health insurance, this possible explanation does not suffice for our cohort. In line with our results no differences in colectomy rates were found between Asians and Caucasians, but interestingly a subgroup analysis across ethnic groups between Indian, Pakistani, Bangladeshi (Asians), and Caucasians did show significant differences in colectomy rates.[25]

Difference in age of onset IBD between non-CEU IBD patients born in Europe compared with non-CEU IBD patients born in non-European countries

Changes in lifestyle, such as a Westernised diet, have been implicated to play a role in the aetiology of IBD.[4-6] In our cohort, we were able to assess the effect of exposure to a Western lifestyle. We found that IBD patients with non-CEU descent born in Europe were diagnosed with IBD at a lower age. This important finding made us speculate that a Western lifestyle might trigger IBD onset more early in life in a genetic susceptible patient; however we were not able to deduce a causal relationship. We realise that the patients in our non-CEU IBD population are genetically very heterogeneous; with most patients having mixed descent (*n* = 72), being African (*n* = 37), or Hindustani (*n* = 37). On the other hand, the non-CEU IBD patients born in non-European countries all have been exposed to a non-Western lifestyle before migrating to the Netherlands. We were not able to address at what age the patient migrated to the Netherlands or whether the diagnosis of IBD was diagnosed in the Netherlands or country of birth. Although phenotype differences were studied in a large cohort with a total of 2921 CEU IBD patients, we had a relatively lower total number of 233 non-CEU IBD patients. It was therefore not possible to conduct a statistical analysis with enough power to detect differences associated with a particular non-CEU population or in a particular non-European country. Still, IBD research in other ethnicities than patients with an European ancestry is of utmost importance and is currently almost non-existent (except for Asia).[26] It has been established that socioeconomic status is associated with IBD risk.[27,28] Unfortunately, we had no data on the socioeconomic status at our disposal.

In conclusion, this study shows that both ethnicity and country of birth are associated with different phenotypes in IBD patients. Furthermore, we found that non-CEU IBD patients born in Europe, exposed to a Westernised lifestyle, have an earlier age of onset compared with non-CEU IBD patients born outside Europe. In clinical practice, clinicians should be aware of distinct phenotype characteristics in the non-CEU IBD populations.

Supplementary Data

Supplementary data are available at *ECCO-JCC* online.

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